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BY EDWARD MELLANBY, M.A., M.B. (CANTAB.).

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CONTENTS.

1. *Previous Work.*

The metabolic changes of pregnancy have been studied by various workers, principally from the point of view of comparing the total output of nitrogenous material with food intake.

The following results may be taken as proved:—

(1) There is a marked rise in the output of nitrogen following childbirth. Grammatikati (1), Zacharjewsky (2), and Slemons (3), among other workers, have definitely proved this.

(2) This increased nitrogen output more than counterbalances the nitrogenous intake, so that women, at this time, lose nitrogen. This is in marked contrast to the storage of nitrogen taking place before delivery.

The explanations offered by the various workers on these points vary considerably. Heinrichsen (4), Zacharjewsky (2), and Longridge (13) ascribe the increased nitrogen excretion to regressive changes in the puerperal woman, particularly changes affecting the uterus. Grammatikati (1) thought it was to be explained by mammary gland changes, more especially by the formation of milk fat from protein and the excretion of the nitrogenous residue.

One other point of interest observed by Slemons (3) is that the total nitrogen of the urine is less on the day of delivery than any other day and that the drop is greater the more prolonged the labour.

As for the individual nitrogenous substances excreted at this period but little is known. Ammonia, which forms a larger percentage of the total nitrogen with the advancement of pregnancy, gradually diminishes to the normal amount. Urea, as might be expected, forms the greater part of the increased nitrogenous excretion following childbirth and, according to Grammatikati, is a maximum when milk appears in the breast and diminishes with the weaning of the child. Other observers have not been able to corroborate this observation or to ascribe the causal connection between urea excretion and milk formation advanced by Grammatikati.

The appearance of creatin in the urine of lying-in women was first observed by Shaffer (5) and in dogs by Murlin (6). The present account is more particularly connected with this excretion of creatin by puerperal women. The analysis of such a condition seemed likely not only to furnish important results as to the life history of creatin, but also to shed light on the strange metabolic changes taking place in the body at this time.

2. *The Relation of the Puerperal Creatin Excretion to the Involution of the Uterus.*

Other well recognised conditions in which creatin is excreted include inanition and cancer of the liver (14), and since a striking feature about these conditions is the rapid wasting of the patient, it has been assumed that when the voluntary muscle breaks down, creatin is liberated into the blood-stream and excreted. This explanation was extended by Shaffer (5) to explain the puerperal excretion of creatin, but, in this case, the muscular tissue supposed to supply the creatin to the blood-stream was not the voluntary muscle but the involuntary muscle of the uterus. A serious difficulty, however, prevents the acceptance of this explanation, in that, while voluntary muscle contains abundant creatin, uterine muscle is quite devoid of this substance. In a previous paper (14), it was pointed out that creatin has a very limited distribution in nature and can only be found in the cross-striated muscle of vertebrate animals. The cross-striated muscle of invertebrates such as the lobster and the king crab, and, on the other hand, the smooth muscle of vertebrates, represent types of muscle which contain no creatin. Consequently, creatin cannot be found in the smooth, unstriated muscle of the uterus. It has been maintained that creatin and creatinin are present in tissues like the uterus because extracts of such tissues frequently give the Weyl or the Jaffé colour reactions. Both these colour tests are given by so many other substances that they are unreliable* as proofs of the presence of creatinin.

* Weyl's colour test with sodium nitroprusside and caustic soda is also given by aldehyde, acetone, acetophenone, and aceto-acetic acid.

Jaffé's colour test with picric acid and soda is given by any reducing agent.

The red colour, which may be developed by mixing extracts of uterine muscle with alkaline picric acid, disappears rapidly on dilution, and cannot, therefore, be due to creatinin. Consequently, Shaffer's explanation, as it stands, does not adequately explain the puerperal excretion of creatin. However, it is possible that, although uterine muscle contains no creatin, yet some substance is present in the muscle which is converted into creatin when that tissue involutes, and appears ultimately in the urine. In order to test this point, the following observations were made.

In a lying-in ward two women were delivered of children by Cæsarian section, the one case (A) because of a contracted pelvis, the second case (B) because of a ruptured uterus. At the time of operation the uterus in Case A was stitched up and retained, while in Case B, with the ruptured uterus, it was completely removed. If the involution of the uterus is accountable for the *post-partum* excretion of creatin, then it is clear that Case A would excrete much more creatin than Case B, where there was no uterus to involute.

A. Cæsarian Section. Uterus stitched up and retained.
Operation January 13, 1910.

	Vol.	Total creatin.	Total creatinin.	$\frac{\text{Creatin}}{\text{Creatinin}}$.
	c.c.	grm.	grm.	
Jan. 14	815	0·987	1·03	0·96
„ 15	650	0·87	0·91	0·95
„ 16	450	0·58	0·54	1·08
„ 17	650	0·72	0·7	1·03
„ 18	1200	0·7	0·97	0·72
„ 19	1650	0·7	0·86	0·89

B. Cæsarian Section. Uterus removed.
Operation January 16, 1910.

	Vol.	Total creatin.	Total creatinin.	$\frac{\text{Creatin}}{\text{Creatinin}}$.
	c.c.	mgrm. in 10 c.c.	mgrm. in 10 c.c.	
Jan. 17	Spec.	9·7	10	0·97
		grm.	grm.	
„ 18, „ 19, „ 20	2500	3·8	1·75	2·13
„ 21	1270	1·76	1·27	1·38

These figures show that the removal of the uterus did not prevent the excretion of creatin, and in fact, Case B, where there was no uterus to

Fortunately, creatinin has a much more potent action than other physiological reducing agents and carries on the reaction very quickly with the formation of di-amino-mononitrophenol—a red substance which retains its intensity on strong dilution. The end product of such reducing agents as dextrose, levulose, maltose, aldehyde, is generally mono-aminodinitrophenol, which is also a red substance, but loses all colour intensity on dilution [Chapman (15)].

This explains why the full dilution of Folin's method of estimating creatinin is absolutely essential; for it is clear that on small dilution the colour of the mono-amino-dinitrophenol will interfere with that of diaminomononitrophenol. This point concerning dilution is a common source of error in recent research on creatinin.

involute, excreted much larger quantities of creatin. It would be unfair to press the interpretation of these experimental figures too far, because I think the excretion of creatin following a Cæsarian section may not be completely analogous to that accompanying a normal pregnancy. For instance, the following figures show that, even after an abdominal hysterectomy for uterine fibroids, creatin is excreted :—

Abdominal Hysterectomy. Fibroids of Uterus.

Time after operation.	Creatin in 10 c.c.	Creatinin in 10 c.c.	$\frac{\text{Creatin}}{\text{Creatinin}}$.
	mgrm.	mgrm.	
18 hours	9·9	14·0	0·7
4 days............	16·0	12·8	1·25
8 „	4·3	9·6	0·45

It may further be stated that all abdominal operations result in the excretion of some, but very variable amounts of creatin: The significance of this fact will be considered elsewhere.*

As regards the Cæsarian section figures two points are worthy of mention.

(1) Although such large amounts of creatin were excreted, the creatinin excretion was normal or but little diminished. In other words, the large creatin excretion was not produced at the expense of the creatinin. For instance, Case B excreted 2·86 grm. of (creatin + creatinin) per diem on an average over three days, whereas in normal health such a woman would excrete but little more than 1 grm. of creatinin and no creatin. This point is important, because it is commonly said that creatin is converted into creatinin, probably by the liver, and also that an increase of creatin excretion is accompanied by a diminution of creatinin. This relation may possibly hold in conditions like inanition, and in the absence of carbohydrate (Cathcart, 7) from the diet, for in such conditions there is usually a diminution of creatinin excreted, together with an increase of creatin. But it does not hold in the above cases of Cæsarian section.

(2) The creatin excretion following Cæsarian section did not depend on inanition or absence of carbohydrate from the diet. Both patients were taking an adequate amount of food throughout the period of examination and the urine did not indicate any condition of acidosis.

To sum up, there is no evidence that the puerperal creatin excretion depends, to any extent, on the involution of the uterus.

* In the meantime I should like to utter a warning with regard to the interpretation of experiments on creatin metabolism which involve opening up the abdominal cavity.

3. *Evidence of the Relation between the Puerperal Excretion of Creatin and Mammary Gland Activity in Women.*

Pregnant rabbits, like pregnant women, excrete abnormal quantities of creatin. In fact the estimation of the creatin in the urine of a rabbit is a useful means of diagnosing pregnancy. It may be well to state that in my experience all rabbits, male and female, excrete small quantities of creatin. Oxen also, independently of sex differences, normally excrete creatin in addition to creatinin. This observation, affecting herbivorous animals, is in marked contrast to the total absence of creatin from the urine of normal people. When I started to investigate the puerperal excretion of creatin, rabbits seemed to be the best animals for examination. It was surprising, however, to find that the excretion of creatin by rabbits stops immediately after delivery, and consequently they were useless for this investigation. One possible factor suggested itself as an explanation of this difference between rabbits and human beings, namely, that rabbits eat their placentæ after delivery. It might be imagined that the proper performance of the functions of the organism after parturition depended upon the presence of certain chemical groupings, which were supplied by the digestion and assimilation of the placenta; but that, in the human being, since no placenta was available, the substances had to be supplied at the expense of other tissues such as the muscles, with the result that creatin was liberated and excreted at the time of the transference of material. If natural craving for animal food is any indication of physiological needs, then it is certain that female animals require the chemical substances of tissues such as muscle after parturition. The longing which such women have for meat has its analogy in the lower animals in their eating placentæ and frequently their young. In the case of herbivorous animals this seems to be the only time in their lives that they are carnivorous and may have some special significance such as the urgent requirements of the animal organism for substances such as extractives.

From this point of view, therefore, a cow was allowed to eat its placenta after parturition, in order to see whether the creatin excretion would be suppressed. The following figures were obtained:—

Cow.

	Creatinin in 10 c.c.	Creatin in 10 c.c.	Creatin / Creatinin.
	mgrm.	mgrm.	
June 2	6 ·0	2 ·7	0 ·45
„ 3	8 ·0	2 ·6	0 ·325
„ 4	10 ·1	4 ·1	0 ·405
„ 5	9 ·0	3 ·2	0 ·356
„ 6*	8 ·5	3 ·5	0 ·41
„ 7	6 ·6	5 ·3	0 ·8
„ 8	6 ·0	4 ·0	0 ·67
„ 9	6 ·2	3 ·0	0 ·48
„ 10	6 ·0	4 ·3	0 ·71

* Calf born June 6, 4 A.M. Placenta eaten by 10 A.M.

It will be seen that a rise of creatin excretion follows the ingestion of the placenta rather than a fall. Consequently it is unlikely that placenta eating explains the absence of creatin in a rabbit's urine *post partum.*

The investigation was continued on women and this will now be described.

(a) *A Quantitative Relation between Creatin Excretion and Milk Secretion in Nursing Women.*—The women were patients at a lying-in hospital,* and the diet in all cases was creatin-free, in that no meat, fish or meat extracts were given. Such a diet† has great drawbacks because of the desire, mentioned above, which these women have for meat and tasty food. The disappointment at the plainness of the diet often makes them depressed, and the mental condition is soon reflected in the poor progress made by the child either because it is not properly nursed or because the mother's milk is of poorer quality. This difficulty was especially obvious in cases of multiparæ who had been in the lying-in hospital before and were therefore accustomed to plenty of meat. Most of the cases studied, therefore, were primiparæ, in whom this mental depression was not so obvious.

Below are the figures obtained in the examination of four normal cases of childbirth. They were all on the same diet and were living in the same ward under precisely the same conditions.

* The Lambeth Lying-in Hospital, S.E., to the staff of which, and in particular to Dr. J. S. Fairbairn, I wish to express my indebtedness.

† A typical day's diet, though it varied to some extent, was as follows:—Milk 25 oz. gruel 5 oz., cocoa (made of milk) 5 oz., an egg, bread and butter 5 oz. Occasionally live up to 4 oz. was added.

Mrs. St. C., delivered 10.35 A.M., December 9, 1910. Primipara.

	Vol.	N in 5 c.c.	Creatinin in 10 c.c.	Creatin in 10 c.c.	Total N.	Total creatinin.	Total creatin.	$\frac{\text{Creatin}}{\text{Creatinin}}$.	Baby's weight.
	c.c.	grm.	mgrm.	mgrm.	grm.	grm.	grm.		oz.
Before delivery	Spec.	—	5·2	1·2	—	—	—	0·23	—
1st day, up to 6 P.M., Dec. 9 ...	700	0·045	5·6	1·4	6·25	0·393	0·1	0·25	80
2nd ,, ,, 10 ...	1330	0·039	7·4	1·2	10·5	0·985	0·16	0·162	77
3rd ,, ,, 11 ...	970	0·044	9·2	1·4	8·44	0·891	0·136	0·152	75
4th ,, ,, 12 ...	1510	0·039	6·8	2·1	11·8	1·03	0·317	0·310	77
5th ,, ,, 13 ...	1000	0·049	8·1	2·8	9·75	0·81	0·28	0·345	77
6th ,, ,, 14 ...	490 (?)	0·056	9·6	2·7	5·5	0·473	0·133	0·282	78
7th ,, ,, 15 ...	980	0·057	9·9	3·6	11·3	0·97	0·353	0·363	79½
8th ,, ,, 16 ...	340 (?)	0·068	11·0	3·8	4·67	0·374	0·129	0·345	79
9th ,, ,, 17 ...	830	0·052	9·4	3·7	8·64	0·783	0·308	0·394	79½

$\frac{\text{Creatin}}{\text{Creatinin}}$ ratio (after establishment of lactation) = 0·340. Gain in weight of baby during same period = 4½ oz. = 0·75 oz. per diem.

Mrs. Gr., delivered 2.25 P.M., May 25, 1910. Primipara. Baby's weight at birth, 120¾ oz.

	Vol.	N in 5 c.c.	Creatinin in 10 c.c.	Creatin in 10 c.c.	Total N.	Total creatinin.	Total creatin.	$\frac{\text{Creatin}}{\text{Creatinin}}$.	Baby's weight.
	c.c.	grm.	mgrm.	mgrm.	grm.	grm.	grm.		oz.
Before birth	Spec.	—	4·9	trace	—	—	trace	0·0	—
1st day, up to 6 P.M., May 26...	1110	0·026	7·0	trace	5·8	0·777	trace	0·0	114½
2nd ,, ,, 27...	1060	0·062	13·3	trace	13·2	1·41	trace	0·0	111½
3rd ,, ,, 28...	670	0·085	15·0	7·0	11·5	1·01	0·469	0·47	114
4th ,, ,, 29...	450 (?)	0·087	11·6	5·9	7·9	0·52	0·265	0·51	116½
5th ,, ,, 30...	980	0·091	13·5	6·8	17·8	1·32	0·666	0·50	116¾
6th ,, ,, 31...	910	0·089	12·4	6·6	16·3	1·13	0·600	0·53	117½
7th day, up to 6 P.M., June 1...	830	0·09	13·3	3·9	14·9	1·10	0·324	0·29	117½
8th ,, ,, 2...	930	0·085	11·0	4·2	15·8	1·02	0·391	0·38	117½
9th ,, ,, 3...	800	0·09	14·0	4·3	14·4	1·12	0·344	0·31	118

$\frac{\text{Creatin}}{\text{Creatinin}}$ ratio (after establishment of lactation) = 0·427. Increase in baby's weight during corresponding period = 6·5 oz. = 0·93 oz. per diem.

Mrs. Gy., delivered 3.25 P.M., May 24, 1910. Primipara. Weight of baby at birth, $115\frac{3}{4}$ oz.

	Vol.	N in 5 c.c.	Creatinin in 10 c.c.	Creatin in 10 c.c.	Total N.	Total creatinin.	Total creatin.	$\frac{\text{Creatin}}{\text{Creatinin}}$.	Baby's weight.
	c.c.	grm.	mgrm.	mgrm.	grm.	grm.	grm.		oz.
1st day, up to 6 P.M., May 25...	1230	0·024	5·5	1·1	6·0	0·675	0·135	0·2	$109\frac{1}{2}$
2nd ,, ,, 26...	690	0·049	8·3	4·6	6·8	0·575	0·317	0·552	$106\frac{1}{2}$
3rd ,, ,, 27...	560	0·079	10·9	5·8	8·8	0·61	0·325	0·487	$108\frac{1}{2}$
4th ,, ,, 28...	700	0·083	8·5	4·5	11·6	0·595	0·315	0·528	$109\frac{1}{2}$
5th ,, ,, 29...	780	0·084	8·6	5·6	13·1	0·67	0·437	0·650	112
6th ,, ,, 30...	740	0·094	10·0	6·9	13·9	0·74	0·51	0·690	113
7th ,, ,, 31...	1070	0·067	7·5	4·1	14·2	0·80	0·435	0·547	$114\frac{1}{2}$
8th day, up to 6 P.M., June 1...	1020	0·056	6·1	2·3	11·5	0·63	0·235	0·377	$114\frac{1}{2}$
9th ,, ,, 2...	570	0·083	10·4	4·4	9·5	0·59	0·25	0·417	115

$\frac{\text{Creatin}}{\text{Creatinin}}$ ratio (after establishment of lactation) = 0·531. Gain in weight of baby during same period = $8\frac{1}{2}$ cz. = 1·21 oz. per diem.

Mrs. T., delivered 12.55 A.M., May 26, 1910. Multipara (third). Baby's weight at birth, $124\frac{1}{2}$ oz.

	Vol.	N in 5 c.c.	Creatinin in 10 c.c.	Creatin in 10 c.c.	Total N.	Total creatinin.	Total creatin.	$\frac{\text{Creatin}}{\text{Creatinin}}$.	Baby's weight.
	c.c.	grm.	mgrm.	mgrm.	grm.	grm.	grm.		oz.
Before birth	—	—	8	2·3	—	—	—	0·29	—
1st day, up to 6 P.M., May 27...	910	0·031	6·75	2·0	5·6	0·615	0·182	0·27	119
2nd ,, ,, 28...	1100	0·051	8·0	4·6	11·2	0·88	0·51	0·57	120
3rd ,, ,, 29...	700	0·088	12·2	8·5	12·4	0·86	0·595	0·68	123
4th ,, ,, 30...	1280	0·053	6·5	4·1	13·5	0·83	0·51	0·63	128
5th ,, ,, 31...	970	0·055	7·4	3·95	10·7	0·72	0·385	0·53	$130\frac{1}{2}$
6th day, up to 6 P.M., June 1...	1350	0·046	6·2	4·4	12·4	0·84	0·595	0·71	$130\frac{1}{2}$
7th ,, ,, 2...	1490	0·041	4·9	3·2	12·1	0·73	0·477	0·65	131
8th ,, ,, 3...	1040	0·051	6·9	5·1	10·7	0·72	0·55	0·77	$131\frac{1}{2}$
9th ,, ,, 4...	1050	0·050	7·2	3·7	10·5	0·76	0·39	0·51	$132\frac{1}{2}$

$\frac{\text{Creatin}}{\text{Creatinin}}$ ratio (after establishment of lactation) = 0·631. Gain in weight of baby during corresponding period = 13·5 oz. = 1·70 oz. per diem.

The following points are indicated by these figures:—

(1) There is a rapid increase in the nitrogen excreted in the first few days after delivery. This point has been frequently observed before and has been commented upon at the beginning of this paper. It will be noted that the rise usually starts on the second day, but in the case of Mrs. Gy. it is delayed until the fourth day. This variation in different women has also been previously noticed and has not been interpreted satisfactorily, some ascribing it to variations in uterine involution, others to variations in mammary gland activity.

(2) Except possibly for the first day after delivery the excretion of creatinin exhibits its usual constancy.*

(3) The creatin rises in the first few days. Consequently, there is a rise in the $\frac{\text{creatin}}{\text{creatinin}}$ ratio in these days.

(4) An examination of the $\frac{\text{creatin}}{\text{creatinin}}$ ratio of the four cases and a comparison with the rates of progress of the infants indicate that the increase in weight of the children is roughly proportional to the creatin excreted by the respective mothers, thus:

	$\frac{\text{Creatin}}{\text{Creatinin}}$.	Increase of baby's weight per diem.
		oz.
Mrs. St. C.	0·340	0·75 (Baby St. C.)
„ Gr.	0·427	0·93 (Baby Gr.)
„ Gy.	0·531	1·21 (Baby Gy.)
„ T.	0·631	1·70 (Baby T.)

It may be stated that the children were entirely breast-fed, so that whatever increase in weight they experienced was due to the milk secreted by the mother's mammary glands. Consequently, the above figures indicate that the $\frac{\text{creatin}}{\text{creatinin}}$ ratio of the urine is related either to the quantity or quality, or both, of the milk secreted by the mammary glands of the mother. In keeping also with this interpretation is the fact that the $\frac{\text{creatin}}{\text{creatinin}}$ ratio increases *pari passu* with mammary gland activity in the first two days after delivery, at a time when the colostrum is being changed to milk.

It is evident that, in order to establish the hypothesis of a relation between

* This constancy is such that when there is any great diminution in a day it may usually be assumed that the 24 hours' specimen is not complete.

creatin excretion and mammary gland activity, other evidence, in addition to that offered, is necessary. It would be advantageous if, for instance, it were possible to calculate directly the amount of milk secreted by a nursing woman. This was not found to be possible. The following indirect evidence, however, may now be considered:—

(b) *A Case of Creatin Excretion and Mammary Gland Activity developing late after Childbirth.*—The next point to be observed is that when a woman's breasts have their activity delayed, following childbirth, then there is a corresponding delay in the creatin excretion. This patient* may be described as a case suffering from a toxæmia of pregnancy, and showed the characteristic symptoms of this condition, namely, general œdema, headache and occasional temporary attacks of blindness. She also excreted much albumen. She never had any eclamptic fits; and, although very ill, labour was not induced, but came on naturally at the end of the eighth month. At the birth of the child the breasts were soft and without any trace of activity. They became gradually active about the fourth day after delivery, and at this time also creatin, which had been, up till this time, quite absent, began to appear and increase.

Mrs. T. (toxæmia of pregnancy). Weight of baby, $3\frac{1}{2}$ lb. Eighth month.

Date.	$\frac{\text{Creatin}}{\text{Creatinin}}$.	Albumen (by Esbach), approximate.
		grm.
February 2	Trace of creatin	—
" 7	" "	—
" 12	" "	7·7
" 15	" "	4·77
" 16*	" "	5·17
" 17	" "	4·03
" 18	" "	4·6
" 19	0·15	0·06
" 20	0·21	1·9
" 21	0·35	0·46
" 22	0·36	0·0
" 24	0·57	0·0
March 2	0·3	
" 5	0·18	
" 8	0·16	

* Time of delivery, February 16, 10 A.M.

In this case the creatin excreted was too small to be estimated until the third day after delivery.

* The case was met with in an investigation of the toxæmias of pregnancy, undertaken in conjunction with Dr. J. P. Hedley.

On February 18, 5 drops of colostrum were squeezed from the breasts.
19, ½ oz. colostrum was withdrawn in the morning. By 6 P.M. 1 oz. could be withdrawn every two hours.
20, lactation established.

As this baby was too feeble to suck, the milk had to be first withdrawn from breasts.

It is interesting to compare the creatin excreted by this toxæmic patient with that of a normal case of pregnancy where labour came on prematurely at the eighth month. She was in good health, and nursed her baby from the first.

Mrs. B. (normal case). Premature labour. About eighth month. Weight of baby, 5¼ lb.

Date.	Creatin / Creatinin.
February 7	0·29
" 14*	—
" 15	0·22
" 16	0·31
" 17	0·34
" 18	0·78
" 19	0·49
" 21	0·27
" 23	0·28

* Baby born February 14.

In this case the creatin excretion was always present, and increased, as after the birth of normal full-term children, for a few days. This is in marked contrast to the case of Mrs. T., where the creatin is absent before delivery, and until the breasts become active. Another interesting point about this toxæmic case is that the appearance of creatin synchronises with a large decrease of albumen in the urine. It appears as if the cause of the albuminuria was also the cause of the suppressed creatin excretion. A similar case of toxæmia of pregnancy has been met with.

(c) *A Case Illustrating Simultaneously Suppressed Creatin Excretion and Mammary Gland Activity.*—Another piece of evidence that creatin excretion and mammary gland activity are related is as follows: if a condition arises, in the first few days after milk secretion is fully established, to suppress the milk secretion, then the creatin excretion stops at the same time.

In the following case, N. was delivered of a baby on May 25. The milk was abundant, and the child developed very well until June 1, when the left breast developed an abscess, and the temperature rose to 102°. This

Mrs. N., delivered 12.15 A.M., May 25, 1910. Primipara. Weight of baby at birth, 106 oz.

	Vol.	N in 5 c.c.	Creatinin in 10 c.c.	Creatin in 10 c.c.	Total N.	Total creatinin.	Total creatin.	$\frac{\text{Creatin}}{\text{Creatinin}}$.	Baby's weight.
	c.c.	grm.	mgrm.	mgrm.	grm.	grm.	grm.		oz.
Before labour........................	Spec.	—	6·8	2·3	—	—	—	0·34	—
1st day, up to 6 P.M., May 25...	242	—	4·65	1·2	14·1	1·13	0·292	0·26	104¾
2nd ,, ,, 26...	680	0·077	10·0	6·1	10·5	0·68	0·415	0·61	99½
3rd ,, ,, 27...	960	0·072	9·0	5·4	13·8	0·865	0·52	0·60	99½
4th ,, ,, 28...	690	0·076	9·0	4·2	10·5	0·62	0·29	0·47	102
5th ,, ,, 29...	880	0·08	9·4	3·7	14·1	0·83	0·325	0·39	103
6th ,, ,, 30...	790	0·088	9·3	5·4	14·0	0·74	0·43	0·58	101
7th ,, ,, 31...	950	—	—	—	—	—	—	—	102½
8th day, up to 6 P.M., June 1*	Spec.	—	10·0	2·2	—	—	—	0·22	103
9th ,, ,, 2...	620	0·084	10·8	1·0	10·4	0·67	0·062	0·092	101
10th ,, ,, 3...	650	0·089	11·9	1·0	11·6	0·77	0·065	0·084	103
11th ,, ,, 4...	560	0·083	11·6	0·0	9·3	0·65	0·0	0·0	104½

* Temperature up to 102°, due to mammary gland abscesses. Milk secretion was suppressed, and from this point the baby was hand fed. Note the suppression of the creatin with the development of the temperature.

was followed by abscesses in the right breast. Both breasts were too painful for nursing the child, and, as the result of the abscesses and hyperpyrexia, the secretion of milk was rapidly and totally suppressed.

It might be supposed that, since in this case the creatin excretion and the milk secretion were synchronously suppressed, any case of suppression of milk secretion, produced by the ordinary methods of banding and purgation, would also cease to excrete creatin. This is not the case, as the following figures show :—

M 18. Confined September 5, 1911. Prolapse of cord, still-born child, placenta prævia. Had nursed previous children. Treatment :—Breasts bandaged tightly, two or three purges each day.

	$\frac{\text{Creatin}}{\text{Creatinin}}$.
September 12	0·79
„ 14	0·62
„ 15	0·78
„ 16	0·70

It will be seen that not only is the creatin not suppressed in this case, but is higher than the normal cases of nursing women given above. If, then, the mammary glands in such a case were without milk, and completely flaccid, it would disprove the relation of creatin excretion and mammary gland activity which it has been the object of this paper to establish. In point of fact, on September 16, the breasts of this woman, in spite of all the purgation she had experienced, contained abundant milk, and were hard and knotty.

On September 8 she had a temperature of 100·2°, due, no doubt, to the congestion of the mammary glands. There is no doubt that purgation and breast bandaging do not suppress mammary gland activity in the sense that illness, particularly when there is fever, does. A feverish condition seems to produce very quickly soft, flabby breasts, markedly different from the hard, knotty breasts of a woman treated by purgation. In keeping with this is the fact that in the one case the excretion of creatin is diminished, and, in the other, is as high, or higher, than normal.

4. *The Effect of Adding Casein to the Diet of a Puerperal Woman.*

Having got some evidence of a relation between mammary gland activity and creatin excretion, the investigation was continued in order to determine whether there is any obvious relation between particular branches of the metabolism of secreting breasts and creatin.

It seemed possible that the *post-partum* excretion of creatin might depend on the metabolic changes taking place in the body which culminate in the formation of caseinogen in the mammary gland at this period. It can be well imagined that the demand of the mammary gland for specific chemical groupings necessary for the formation of caseinogen itself might result in chemical changes, particularly in the muscle, which would cause the liberation of creatin into the blood-stream and its subsequent excretion. If such were the case, then the addition of casein to the diet might render unnecessary the creatin-liberating changes and effect a corresponding disappearance of excreted creatin at this time.

In the two following cases, 50 grm. of casein were added to the creatin-free diet each day.

It is evident that there is no diminution of creatin excreted as the result of casein feeding, and the results lend no support to the hypothesis that the metabolic changes involved in the formation of caseinogen by the mammary gland are related to the *post-partum* excretion of creatin.

5. *The Independence of the Puerperal Excretion of Creatin and Carbohydrate Metabolism.*

The *post-partum* excretion of creatin is a good example of the fact that there may not be anything, so far as is known, wrong or abnormal with carbohydrate in the body while at the same time large quantities of creatin are being excreted.

Needless to say there is no acidosis in the case of a normal pregnancy, so any relation between creatin excretion and carbohydrate is not so obvious as such a condition would signify. For it is probable that all cases of acidosis are accompanied by the excretion of some, although widely variable amounts of, creatin. It seemed likely that the carbohydrate abnormality responsible for the creatin excretion at this period was not an absolute deficiency of carbohydrate in the body, but rather a sidetracking of certain constituents of the carbohydrate in order to furnish an adequate supply of lactose-forming substances to be dealt with by the mammary gland. Consequently in the two cases now to be described lactose and dextrose were respectively added to their otherwise abundant diets in order to satisfy any glycogen and dextrose deficiency of the liver, and also the lactose requirements of the mammary gland.

It is obvious from these two carbohydrate-feeding experiments that if there is any connection between carbohydrate and creatin excretion during puerperium, it is obscure and of such a nature that alimentary carbohydrate plays no part in the relation. In neither case—lactose feeding and

Mrs. M. Primipara. Baby born 3.40 P.M., January 15, 1911.

	Vol.	N in 10 c.c.	Creatinin in 10 c.c.	Creatin in 10 c.c.	Total N.	Total creatinin.	Total creatin.	$\frac{\text{Creatin}}{\text{Creatinin}}$.	Weight of baby.
	c.c.	grm.	mgrm.	mgrm.	grm.	grm.	grm.		oz.
1st day, up to 6 P.M., Jan. 16...	1250	0·052	4·5	1·51	6·54	0·564	0·189	0·336	100
*2nd ,, ,, 17...	1180	0·070	5·5	2·56	7·93	0·62	0·288	0·465	98½
*3rd ,, ,, 18...	810	0·091	6·3	3·14	8·06	0·555	0·276	0·498	98
*4th ,, ,, 19...	1680	0·087	4·8	2·44	14·7	0·808	0·41	0·51	99
*5th ,, ,, 20...	910	0·107	5·4	1·99	9·75	0·493	0·181	0·368	99½
*6th ,, ,, 21...	1150	0·172	7·7	3·25	19·8	0·886	0·373	0·422	102½
*7th ,, ,, 22...	1760	0·098	4·3	1·86	17·3	0·757	0·327	0·433	102½
*8th ,, ,, 23...	1200	0·132	5·8	3·72	15·9	0·696	0·446	0·64	102½
*9th ,, ,, 24...	670	0·113	4·9	2·21	7·6	0·328	0·148	0·45	104
*10th ,, ,, 25...	1240	0·083	3·4	2·20	10·3	0·423	0·273	0·65	105½
*11th ,, ,, 26...	670	0·158	6·9	3·25	10·6	0·464	0·218	0·472	107

Baby entirely breast fed. $\frac{\text{Creatin}}{\text{Creatinin}}$ (from time of establishment of lactation) = 0·493. Increase of weight of baby per diem = 1·12 oz.

* 50 grm. of casein to mother, in addition to creatin-free diet.

Mrs. A. Primipara. Baby born 6.55 A.M., January 17, 1911.

	Vol.	N in 10 c.c.	Creatinin in 10 c.c.	Creatin in 10 c.c.	Total N.	Total creatinin.	Total creatin.	$\frac{\text{Creatin}}{\text{Creatinin}}$.	Weight of baby.
	c.c.	grm.	mgrm.	mgrm.	grm.	grm.	grm.		oz.
1st day, up to 6 P.M., Jan. 17...	250	—	7·5	1·28	—	0·184	0·032	0·17	100
*2nd ,, ,, 18...	1170	0·09	8·0	1·86	10·5	0·94	0·217	0·232	96
*3rd ,, ,, 19...	570	0·142	9·6	4·65	8·1	0·55	0·265	0·483	93½
*4th ,, ,, 20...	900	0·112	7·2	4·07	10·1	0·65	0·367	0·563	91
*5th ,, ,, 21...	860	0·113	6·0	3·83	9·74	0·517	0·33	0·638	93½
*6th ,, ,, 22...	1160	0·131	6·3	3·60	15·2	0·73	0·418	0·572	94
*7th ,, ,, 23...	810	0·136	7·2	3·95	11·0	0·584	0·32	0·55	95½
*8th ,, ,, 24...	640	0·153	7·4	4·3	9·8	0·475	0·275	0·58	97
*9th ,, ,, 25...	—	0·159	8·0	5·1	—	—	—	0·64	98½
*10th ,, ,, 26...	1390	0·087	5·9	3·02	12·1	0·82	0·42	0·51	96½†
11th ,, 6 A.M. ,, 27... (12 hrs.)	380	—	6·8	2·44	—	—	—	0·36	98½

$\frac{\text{Creatin}}{\text{Creatinin}}$ ratio (after establishment of lactation) = 0·55. Increase in weight of baby = 7½ oz. in 7 days = 1·07 oz. per diem.

* On these days 50 grm. of casein added to diet.

† The loss in weight on this day may probably be accounted for by the development of whitlows on thumb and first finger of the mother, which had to be treated.

Mrs. N., delivered 2 P.M., December 8, 1910. Multipara (two).

	Vol.	N in 10 c.c.	Creatinin in 10 c.c.	Creatin in 10 c.c.	Total N.	Total creatinin.	Total creatin.	$\frac{\text{Creatin}}{\text{Creatinin}}$.	Baby's weight.
	c.c.	grm.	mgrm.	mgrm.	grm.	grm.	grm.		oz.
Before birth	Spec.	—	8 ·4	2 ·5	—	—	—	0 ·297	—
1st day, up to 6 P.M., Dec. 9...	1020	0 ·077	7 ·7	3 ·1	7 ·88	0 ·787	0 ·317	0 ·403	107
*2nd ,, ,, 10...	Spec.	—	11 ·4	5 ·1	—	—	—	0 ·447	102½
*3rd ,, ,, 11...	1030	0 ·13	11 ·1	6 ·5	13 ·4	1 ·15	0 ·673	0 ·585	104½
*4th ,, ,, 12...	1170	0 ·112	7 ·4	4 ·9	13 ·1	0 ·867	0 ·575	0 ·663	108
*5th ,, ,, 13...	360 (?)	0 ·173	11 ·4	7 ·7	6 ·28	0 ·411	0 ·277	0 ·675	111
*6th ,, ,, 14...	550	0 ·147	9 ·6	5 ·6	8 ·1	0 ·528	0 ·308	0 ·582	112
*7th ,, ,, 15...	840	0 ·149	9 ·6	4 ·3	12 ·6	0 ·808	0 ·362	0 ·447	114½
†8th ,, ,, 16...	690	0 ·132	9 ·6	2 ·7	9 ·14	0 ·664	0 ·186	0 ·28	113½
†9th ,, ,, 17...	810	0 ·138	9 ·7	5 ·2	11 ·2	0 ·787	0 ·422	0 ·536	113

During lactose period $\frac{\text{creatin}}{\text{creatinin}}$ ratio = 0 ·566, and increased weight of baby 1 ·57 oz. per diem. The child was entirely breast fed.

* On these days 50 grm. of lactose were added to diet. † On these days 75 grm. of glucose were added to diet.

Mrs. Str., delivered 6.23 A.M., December 9, 1910. Multipara (three).

	Vol.	N in 10 c.c.	Creatinin in 10 c.c.	Creatin in 10 c.c.	Total N.	Total creatinin.	Total creatin.	$\frac{\text{Creatin}}{\text{Creatinin}}$.	Baby's weight.
	c.c.	grm.	mgrm.	mgrm.	grm.	grm.	grm.		oz.
1st day, up to 6 P.M., Dec. 9...	Spec.	0 ·0477	3 ·4	1 ·05	—	—	—	0 ·307	106
*2nd ,, ,, 10...	1730	0 ·055	6 ·1	1 ·51	9 ·53	1 ·05	0 ·262	0 ·247	103
*3rd ,, ,, 11...	960	0 ·112	10 ·5	2 ·56	10 ·7	1 ·01	0 ·246	0 ·243	96½
*4th ,, ,, 12...	700	0 ·115	9 ·0	3 ·26	8 ·07	0 ·63	0 ·228	0 ·362	96½
*5th ,, ,, 13...	480	0 ·084	7 ·2	2 ·56	4 ·83	0 ·346	0 ·123	0 ·355	97½
*6th ,, ,, 14...	740	0 ·0695	5 ·8	2 ·21	5 ·15	0 ·43	0 ·163	0 ·380	99
*7th ,, ,, 15...	1870	0 ·0808	5 ·6	1 ·86	15 ·1	1 ·05	0 ·348	0 ·332	97½
8th ,, ,, 16...	810	0 ·109	7 ·0	2 ·32	8 ·84	0 ·568	0 ·188	0 ·332	97½
9th ,, ,, 17...	1050	0 ·113	7 ·6	3 ·6	11 ·9	0 ·798	0 ·377	0 ·474	96

$\frac{\text{Creatin}}{\text{Creatinin}} = 0 ·334.$ Baby lost weight.

* On these days 75 grm. of glucose (20 grm. to ℥1) were taken by the mother, in addition to ordinary food. The baby was breast fed until December 13, at which time, in consequence of poor progress, alternate feeds of cow's milk and cream were added to diet.

glucose feeding—was the creatin excretion abnormally low, and indeed in the former case the creatin ratio was high.

Another point worthy of comment is the very poor progress of the baby whose mother took glucose. Of all the cases investigated this baby did the worst.* This may have been a coincidence, but there is some evidence that the glucose solution itself had a detrimental effect, in that when it was substituted for lactose in the first case described, this baby's weight began to diminish, although previously it had developed remarkably well. On the two glucose-feeding days it lost $1\frac{1}{2}$ oz. in weight, whereas in the previous two lactose-feeding days, the weight of the baby increased $3\frac{1}{2}$ oz.

Whether or no glucose feeding to a puerperal mother has a detrimental effect in all cases on the development of an adequate mammary gland secretion, the above results quite suffice to demonstrate that the creatin excretion of the puerperium is of a different nature from that excreted during periods of inanition or when carbohydrate is withheld from the diet.

In view of the great amount of attention the relation of creatin to carbohydrate metabolism has in recent years attracted, it may be well to consider briefly this subject with reference to the results obtained in this section. It is generally admitted that if carbohydrate metabolism be abnormal in mammalia, then creatin is excreted. For instance, it has been shown that the creatin excretion produced by inanition can be cleared up by the ingestion of carbohydrate (Cathcart (7), Mendel and Rose (8)). Further, the absence of carbohydrate from an otherwise normal diet results in the excretion of creatin. Also in diabetes mellitus and phloridzin glycosuria (Krause and Cramer (9), Cathcart and Taylor (10)) creatin is excreted. It is natural that such facts have led many physiologists to assign the most intimate relationship between creatin and carbohydrate. For instance, it has been suggested that creatin forms compounds with carbohydrate in the liver, and is transported in such a combination to the muscles. Mendel and Rose (8) have stated that, "without question, the metabolism of creatin is intimately related with carbohydrate metabolism." Now it would appear that all the conditions studied in this connection, either pathological or the result of treatment, have one factor in common, namely, the carbohydrate metabolism is either known to be or is rendered abnormal, and then the creatin excretion is studied. But I venture to suggest that this is not sufficient to establish a direct relation between creatin and carbohydrate. If, as the result of recent metabolic research, one point has become more

* The baby of the glucose-fed mother lost ground so rapidly that artificial feeding was added after the third day, but in spite of this the baby gained no weight so long as the investigation lasted.

prominently emphasised than any other, it is that carbohydrates play a more important part than as simple sources of available energy. Incidentally, it may be mentioned that, even as sources of energy, the work of Landergren (11) made it clear that the body preferred carbohydrate to other substances. The excretion of β-oxybutyric acid and allied bodies in abnormal carbohydrate conditions makes it apparent that carbohydrate is necessary for the adequate performance of katabolic changes of fatty acids. Further, evidence has accumulated, since Lüthje (12) first advocated the theory, to show that carbohydrate is necessary for the synthesis of proteins from the amino-acids by the bioplasm of the animal.

Again, there is abundant evidence from the number of toxic substances, such, for instance, as phenol and camphor, which are excreted by the body in combination with glycuronic acid, that the poison neutralising powers of the body are largely dependent upon carbohydrates. In support of this fact, also, may be mentioned the experiments of Hildebrandt (16), who demonstrated the innocuous effects of an otherwise lethal dose of thymotin piperidid, if administered with dextrose or cane sugar.

These few instances show the importance of carbohydrate in physiological activity, and it would appear that nearly all the metabolic processes of the body, with which we are familiar, become abnormal both when it is absent and when it cannot be used. It is not, therefore, contrary to expectation if creatin metabolism, which is a comparatively recent innovation in biochemical development, and not even constant in different mammals, shows signs of abnormality when the carbohydrate stores become unavailable. But it seems to me that evidence of a different nature to that already adduced must be established before creatin can be as directly related to carbohydrate in the body as some would have us believe.

As regards fatty acid metabolism, it is generally agreed that not only does deficiency of carbohydrate in man necessitate the excretion of β-oxybutyric acid, but also the excretion of this latter substance is a reliable indication of abnormal carbohydrate metabolism. Can this test be applied to creatin and carbohydrate? It is an undoubted fact that abnormal carbohydrate metabolism is accompanied by an excretion of creatin. Does the excretion of creatin mean deficient available carbohydrate? The studies of creatin excretion by puerperal women, above described, lend no support to the view that carbohydrate is not abundant and available. Again, it is impossible to stop herbivorous animals like rabbits and cattle from excreting small quantities of creatin, no matter how much carbohydrate is eaten. Finally, it may be mentioned that the creatinuria in a case of cyclic vomiting recently described (17) could not be cleared up by feeding with

carbohydrate. Such facts as these render it improbable that creatin excretion is, in any sense, an indication of abnormal carbohydrate metabolism, and it seems to be that the causal relationship commonly held to have been established between these two substances is quite unjustified. The situation can be summed up by the statement that creatin metabolism, together with many other biochemical changes in the organism, goes wrong in the absence of carbohydrate, but, on the other hand, an abnormal creatin metabolism does not mean an abnormal carbohydrate metabolism.

6. *General Considerations.*

There is some evidence that the puerperal excretion of creatin depends upon the action of a substance formed in the mammary gland itself. For instance, it was seen above that the woman who did not suckle her child after parturition excreted an abnormally large proportion of creatin. In such a case, when the mammary gland is not freed of its milk in the normal way, any active substance would undoubtedly be absorbed to excess into the blood-stream from the gland, and an excessive excretion of creatin result.

Just as the ovum at an early stage of development must produce some potent physiological substance in order to alter the disposition of nutriment in the maternal organism for its own benefit, so the mammary gland, after childbirth, must use equally powerful means to force its claim upon a community of cells, each fighting for the good things distributed by the blood. The potency of the substances formed in the early fœtus is evident in the morning sickness and other unpleasant symptoms of pregnancy, while, on the other hand, there is evidence of a similar nature that the mammary glands immediately after childbirth contain physiologically active substances. For instance, the milk fever of cows is a condition for which the mammary glands are largely responsible.* That this is so is evident by the treatment of the condition, a treatment which generally brings about recovery, namely, to inflate the udders with air. Such treatment suppresses the activity of the mammary gland, and, no doubt, stops the formation of the active toxic substances.

Somewhat analogous to the milk fever of cows is the very common pyrexia seen in women about the third day after childbirth, more especially in those women where the milk secretion is very abundant and the breasts are congested and tender. It is only by careful evacuation of the breasts

* Dr. Pembrey informs me that another important factor in milk fever is the state of nutrition of the cows. Pregnant cows which have been overfed are much more liable to milk fever.

that pyrexia is avoided at these times, and the cause of the fever is undoubtedly some substance formed in the mammary gland and absorbed in excess into the general circulation. It may be that the substance formed in the mammary gland and responsible for the pyrexia of the puerperium may also account for the creatin excretion at this period and the great metabolic changes which result in the transference of nutrient material to the breasts. Another hypothesis which links up the same facts is that toxic substances may be formed as waste products in the mammary gland and ovum at early stages of development and that these substances cause the excretion of creatin. Certainly, in several cases where there was slight pyrexia after parturition, associated with mammary gland congestion, I found a high $\frac{\text{creatin}}{\text{creatinin}}$ ratio in the urine. Such an explanation, also, would fall into line with the fact that the best milking mothers excreted the most creatin.

The fact that creatin is also excreted during pregnancy indicates that there is nothing specific about the probable relation of creatin excretion and mammary gland activity. In the adult person it seems to be a general reaction indicating some abnormal condition affecting the transport of nutrient material, such, for instance, as that which must accompany the growth of a fœtus* or the development of milk secretion. Such a generalisation would include the metabolic condition of carbohydrate deficiency, where, again, creatinuria is present. Also, the results of Mendel and Rose (18), who observed the excretion of creatin in all stages of childhood and adolescence, suggest the association of creatin with the transport of material necessary for the growing tissues.

In most of the other conditions brought to light in which large quantities of creatin are excreted, it has been possible to show that the liver is primarily affected: such conditions for instance as cancer of the liver, deficiency or abnormality of carbohydrate metabolism, toxæmias directly affecting the liver as when a septic focus is in the abdominal cavity, and after operative interference with parts of the body supplied by the portal circulation.† It has not been possible to get any evidence of liver abnormality in the case of lactating women, but, by analogy, it might be expected that here also the liver holds the key to the situation.

The conditions in which creatin is excreted may be divided into two groups.

* We are endeavouring to find out whether there is any relation between the creatin excretion of a pregnant woman and the development of the fœtus.

† These latter two conditions I shall consider elsewhere.

(1) Where the creatinin excreted is normal, as in pregnancy, the puerperal period, and childhood.

(2) Where the creatinin excreted is markedly subnormal, as in starvation and cancer of the liver.

In the first cases the muscle apparently retains its normal nutrition, and in the second cases there is rapid wasting. In fact, it seems likely that creatinin excretion is both an indication and a measure of the transport of material from the liver to the muscles. When this transport breaks down completely, as in carbohydrate deficiency, or when nutrient material is shunted off to supply a neoplasm in the liver, or a growing fœtus, or a developing mammary gland, then creatin is excreted. It is, at least, safe to say that most of the recent evidence of the part played by creatin and chemically allied substances which go to form the group known as "extractives" tends to show that they are concerned with the direction of nutritional transport and tissue synthesis, and that they are neither the source nor an indication of katabolic energy changes, as it has been so long supposed. As for the early period of lactation considered in this paper, the evidence leads one to believe that, in a normal suckling woman, whereas the creatinin excreted indicates the condition of nutrition of her muscles, the creatin excreted is a measure of nutriment conveyed to her mammary glands.

7. *Summary.*

In addition to confirming previous workers as to the mode of excretion of nitrogen by women after childbirth, the following new facts have been brought forward:—

1. The excretion of creatin by women, *post partum*, does not depend upon the involution of the uterus. It was shown that a woman delivered by Cæsarian section, and whose uterus was removed at the time of operation, excreted more creatin than another Cæsarian section case whose uterus was left intact.

2. Rabbits do not excrete creatin at this period. The explanation is not obvious. Eating the placenta does not explain the difference, for a cow, after having eaten its placenta, excreted large quantities of creatin.

3. A metabolic study of parturient women on creatin-free diets indicates that the creatin excretion at this time has some relation to mammary gland activity.

(*a*) There is a gradual increase in the $\frac{\text{creatin}}{\text{creatinin}}$ ratio in the first few days after delivery, corresponding with the increased mammary gland activity and the development of milk from colostrum.

(*b*) The increase in weight of healthy children breast fed under similar normal conditions is roughly proportional to the amount of the creatin in the mother's urine. In other words, the creatin excreted in the urine seems to have some relation to the nutriment given by the mother to her child.

(*c*) If owing to a toxæmic condition the activity of the breasts is delayed after childbirth, the creatin excretion is also delayed, and both develop synchronously in such cases.

(*d*) The early suppression of mammary gland activity by the development of fever and mammary gland abscesses is accompanied by the suppression of the creatin excretion. On the other hand, purgation and bandaging do not diminish the creatin excretion of the puerperium. Nor do they suppress mammary gland activity in the same way as illness does, for the breasts remain hard and knotty, and milk can usually be squeezed out for a considerable time after such treatment.

4. Feeding with casein does not affect the creatin excretion of a parturient woman.

5. The *post-partum* excretion of creatin is dissimilar from that accompanying acidosis and lack of carbohydrates. Lactose and glucose, added to the diet, do not appear to affect the creatin excretion.

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